**An Overview on Novel Liposphere Drug Delivery System: Current Scenario**

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**ABSTRACT**

Topical delivery offers a non-invasive and simple alternative to the traditional delivery method for both systemic and topical drug administration. The biggest obstacle to successfully delivering medication molecules to the deeper layers of skin for systemic absorption is the skin's significant imperviousness. Numerous approaches have been explored to enhance the efficacy of drug delivery across the epidermal barrier. Lipid-based colloidal carriers have garnered significant attention due to their ability to interact with the skin's lipid-rich composition, facilitating transdermal drug administration. Through their attachment to the skin, these carriers facilitate the exchange of lipids in the stratum corneum's outer layers. Even though lipid-based systems have been the subject of many investigations, a thorough literature search turned up no particular talks regarding their transdermal absorption and possible toxicity. The difficulties of transdermal drug delivery, the function of lipid-based vehicular systems in aiding this procedure, uptake mechanisms, sequential uptake processes, and worries about the cytotoxicity of lipid-based carriers—which, despite being widely regarded as safe, may not be completely free from toxicity—are therefore the main topics of this review.Top of Form

***Key words:*** Topical delivery, lipospheres system, corneum, epidermis, phospholipids, law of diffusion etc.

1. **INTRODUCTION**

Novel drug delivery systems have provided a new direction towards controlled and targeted drug delivery. The liposphere drug delivery system is one of these technologies that has been acknowledged as a practical means of delivering medication to the bloodstream. For a number of therapeutic inductions, topical medication transport via the skin to the systemic circulation offers a practical method of administration.1

**A. Barrier Limiting Topical Lipospheres Delivery**

**a) Skin**

The delivery of drugs to the skin offers an efficient and targeted approach for treating both local and systemic disorders. This method of drug delivery has become increasingly popular due to its ability to bypass first-pass effects, reduce gastrointestinal irritation, and minimize metabolic degradation that often accompanies oral administration. Topical formulations serve as an ideal drug delivery system because they are less oily and can be readily removed from the skin.2

**b) Anatomy and Physiology of Skin 3**

The skin plays a pivotal role as the primary barrier for the topical delivery of drugs. To grasp the fundamentals of topical drug delivery systems, it is essential to delve into the structural and biochemical characteristics of human skin that govern its barrier function and the rate at which drugs can penetrate into the body through the skin. In adults, human skin spans an impressive surface area of approximately 1.5 to 2 square meters and exhibits a thickness ranging from 0.5 mm to 2 mm. It comprises four distinct layers: the stratum corneum, viable epidermis, dermis, and subcutaneous tissue. This skin envelope envelops the entire body and maintains seamless continuity with the membranes that line the body's orifices.

* It protects from injury and from invasion by microbes.
* It contains sensorynerve endings of pain.
* It is involved in the regulation of body temperature.

**c) Stratum Corneum**

Elevated hydrophobicity is a characteristic of the stratum corneum, the skin's thick outermost layer. This layer is rich in neutral lipids like cholesterol, fatty acids, and cholesteryl esters but lacking in phospholipids. These lipids are arranged in a bilayer configuration, which results in the formation of 'lipid channels.'

**d) Epidermis**

The main component of the skin's outermost layer, the epidermis, is stratified keratinized squamous epithelium. It is thickest on the palms of the hands and the soles of the feet, and it is not nerve endings or blood vessels. Intracellular lipid channels and partitioning and solubility phenomena are directly linked to the vital role of the viable epidermis in preserving the integrity of the skin barrier. As drugs diffuse through the stratum corneum, they can partition from one layer to another. Additionally, the epidermis contains various cell types, including melanocytes, Langerhans cells, dendritic T cells, and epidermotropic lymphocytes.

**e) Dermis and Hypo Epidermis**

The dermis is elastic and hardy. Its matrix, which is made of connective tissue, has collagen and elastic fibers entwined in it. Varying levels of adipose tissue and areolar tissue make up its lowest layer. The dermis is primarily a layer with a high concentration of nerve endings, lymphatic vessels, and blood vessels. The systemic circulation is linked to a vast network of dermal capillaries, which branch off from the venules and arterioles in the papillary dermis to create plexuses and provide capillaries to glands and hair follicles. The skin's lymphatic veins aid in removing antigenic compounds and removing extracellular fluid. Collagen and elastin are two of the protein fibers that make up the dermis's network and are responsible for its suppleness. Leukocytes, mast cells, macrophages, and fibroblasts are also sporadically found in the dermis. The dermis contains sweat glands, sebaceous glands, and hair follicles.

**f) Mechanism of Topical Drug Delivery 4**

When a medication delivery system is applied topically, the medication diffuses into the skin's surface from its vehicle. Substances appear to be able to easily enter the circulation through capillaries once they have penetrated the stratum corneum, leaving the remaining epidermal layers and corneum unhindered. At the onset of circulation, the concentration gradient virtually terminates in the dermal layer. For cells in the stratum corneum, there is insufficient evidence to establish unique active transport mechanisms. Only the substance being absorbed, the medium in which the substance is disseminated, and the surrounding conditions have an impact on the passive process. The more difficult process of percutaneous absorption consists of two phases: the first is epidermal diffusion, and the second is dermal clearance. The latter is dependent on lymphatics, interstitial fluid mobility, and efficient blood flow.

Ideal properties of drug molecule for topical drug delivery: -

* Low molecular mass, preferably less than 600 Dalton, when diffusion coefficient should be high.
* Adequate solubility in oil and water.
* Membrane concentration gradient should be high.
* Low melting point and it should be correlating with ideal solubility theory.

**g) Physical Chemistry of Drug Absorption**

Skin permeation involves active activities, and simple passive diffusion regulates the transport mechanism. The analysis of medication absorption can be done using Fick's law of diffusion. When describing steady state diffusion, Fick's first law can be defined as:-

 J = DK$∆$C/h

where h is the diffusion path length, ∆C is the concentration change across the skin, k is the skin vehicle partition coefficient, D is the diffusion coefficient in the skin, and J is the flux per unit area. Equation 1 can be simplified to: Since the applied concentration (CAPP) is often significantly greater than the concentration beneath the skin,

 J = KP\*CAPP

Where KP is a permeability coefficient (= KD/h) and is heterogenous rate constant having the units cm/h.

1. **LIPOSPHERES**

Innovative lipid-based encapsulating technologies known as lipospheres are intended for the topical and parenteral administration of particular pharmaceuticals. In the beginning, Domb and Maniar introduced the idea of lipospheres. These formulations are made up of solid spherical particles that are distributed in a certain way and have a solid hydrophobic fat core that can contain fatty acid derivatives or triglycerides. A phospholipid monolayer stabilizes these lipospheres, and the medicine is either dissolved or disseminated within the lipospheres' internal core. Antibiotics, local anesthetics, anticancer medications, and anti-inflammatory compounds are just a few of the substances that lipospheres have been used to deliver. Typically, lipospheres are characterized by solid, water-dispersible particles with diameters ranging from 0.1 to 100 μm. Their advantageous features encompass excellent physical stability, high dispersibility in aqueous media, minimized mobility of incorporated drug molecules, reduced drug leakage, prolonged release of the entrapped drug, biocompatibility, biodegradability, non-immunogenicity, cost-effectiveness, and the capacity to encapsulate a wide array of water-insoluble compounds. Moreover, lipospheres exhibit a strong affinity for vascular walls, inflamed tissues, and granulocytes. Neutral fats such as tricaprin, trilaurin, tristearin, stearic acid, ethyl stearate, or hydrogenated vegetable oil can be used to generate the hydrophobic core. Liposphere formulations use polymers such poly(lactic acid) and polylactide-co-glycoside (PLGA).6

In the lipid formulations for drug delivery, the effect of drug and lipid component of the system on the drug handling processes in the skin, systemic circulation is important. In the lipospheres drug delivery system matter of transit, digestion, solubilisation is necessary to consider. Solubility and partition coefficient of drug between the two types of fatty acid is mainly dependent on the physiochemical properties of the drug. The interaction of lipid formulation with the skin and its bioavailability is present major challenges. Lipids have the ability to improve the lymphatic transport of hydrophobic medications, which can decrease the amount of drug clearance that comes through first-pass metabolism.

**A. Applications of Lipospheres**

A variety of medications, including antibiotics, anticancer medicines, local anesthetics, and anti-inflammatory chemicals, have been delivered under control using the liposphere system. They have also been effectively employed as adjuvant and vaccination carriers. Lately, lipospheres have been employed in the oral medication delivery and peptide delivery systems.7. Compared to alternative distribution methods, lipospheres offer a variety of benefits, including:

* -The absence of coalescence results in increased physical stability in the liposphere.
* Aqueous medium dispersibility is high.
* Less mobility of the integrated drug molecules helps to prevent drug leakage and avoid instabilities caused by the interaction of the drug molecules with the emulsifier layer.
* -Prolonged release of drug entrapment following topical administration.
* -Static interface enables carrier particle surface change following lipid matrix solidification.
1. **FORMULATION OF LIPOSPHERES**
* The liposphere formulation method makes use of naturally existing biodegradable lipid components.9. Triglycerides, in particular, make up the hydrophobic interior core of lipospheres, whilst the polymer layer around the liposphere provides surface activity. The hydrophobic liposphere core is additionally prepared using stabilizers and neutral lipids. The liposphere's lipids and stabilizers. To increase the durability of polymeric lipospheres, a few biodegradable polymers are also utilized in their synthesis. These polymers include:
* Low molecular weight poly(lactic acid)
* Poly (caprolactone)

The phospholipids are used to form the surrounding layer of lipospheres includes:

* Pure egg phosphatidylcholine (PCE)
* Soybean phosphatidylcholine (PCS)
* Dimyristoyl phosphatidylglycerol (DMPG) and
* Phosphatidylethanolamine (PE).
* Food grade lecithin (96% acetone insoluble).
* Lipospheres for topical and veterinary applications.

**A. Technique of lipospheres formulation**

**a) Melt Dispersion Technique**

Both with and without a lipophilic model medication, the lipidic physical combination comprising lipid, phospholipids, cholesterol, etc., is created. After melting the physical combination at 70°C, it is emulsified into a hot, external aqueous phase that is kept at that temperature and contains the appropriate surfactant. The emulsion is kept at 70°C and mechanically agitated using a stirrer fitted with alternating impellers. After that, the emulsion formulation is quickly chilled to roughly 20°C by submerging it in an ice bath while stirring it continuously to produce a homogeneous dispersion of LS. After being obtained, the LS is filtered through a paper filter and rinsed with water.10

**b) Solvent Evaporation Technique**

 This method is being explored as a potential mitigation strategy for the exposure of thermolabile substances, like proteins and nucleic acids, to high temperatures. It is an alternative to the melt dispersion method. The foundation of this method is the evaporation of an organic solvent that dissolves lipids and promotes the creation of solid microparticles. Specifically, the lipidic matrix is dissolved in an organic solvent (ethyl acetate) at a temperature of around 50°C. An external aqueous phase containing the surfactant agent is then added to the dissolved matrix to create an emulsified mixture. After that, the oil-in-water emulsion is agitated for six to eight hours to allow the solvent to completely evaporate. By passing them through filter paper, the LS are retrieved. 11

 **c) Co-Solvent Solvent Evaporation Method**

This co-solvent - solvent evaporation method uses N-methyl pyrrolidone and chloroform to produce a clear solution; however, the resultant big particle size and low yield can be adjusted by varying the solvent employed. Lipospheres composed of polar and non-polar lipids that deviate from the concept of a liposphere as stated by Domb in his patent by employing synthetic stabilizers in place of phospholipids. Even though their research had nothing to do with protein delivery, they did experiment with a hydrophilic medication and found that the double emulsification method could entrap about 50% of the drug.8

**d) Multiple Microemulsion**

This process involves dispersing the peptide solution in stearic acid melt at 70ºC, which is followed by a primary emulsion being dissolved into an aqueous solution containing egg lecithin, butyric acid, and sodium tauro deoxycholate salt at the same temperature (Morel et al., 1994). 90% of the peptide was entrapped in solid lipospheres created by rapidly chilling several emulsions. By using the repeated emulsification process and adding a lipophilic counter ion to create a lipophilic salt of a peptide, sustained release has been described. There have also been reports of using double emulsification to encapsulate antigen in polymeric lipospheres. 12

**e) Sonication Method**

Using this method, a scintillation vial that has been pre-coated with phospholipids is used to combine the medication and lipid. To guarantee that the materials are properly mixed, the vial is heated until the lipid melts and then vortexed for two minutes. The combination above is combined with 10 milliliters of hot buffer solution, which is then sonicated for 10 minutes while being periodically cooled until it reaches room temperature. 13

**f) Roto Evaporation Method**

Using this method, a lipid solution containing the medication is made in a round-bottom flask along with 100 grams of glass beads (3 mm in diameter), which are well mixed to produce a transparent solution. The solvent is then removed using a roto vaporizer set to low pressure at room temperature, forming a thin coating surrounding the glass beads and the flask with a circular bottom. Increase the temperature to 40°C to allow the organic solvent to completely evaporate. The round-bottom flask is filled with a known amount of 0.9% saline, and the contents are mixed for 30 minutes at room temperature. Next, the temperature is dropped to 10°C by placing the flask in an ice bath, and mixing is done for an additional 30 minutes, or until lipospheres develop..14

**g) Microfluidizer Method**

Making lipospheres with a microfluidizer that has two different entrance ports is an additional technique. While a homogenous melting solution or suspension of drug and carrier is pushed from the first entrance port, an aqueous buffer is pumped from the second entry port. To form the lipospheres, the liquids are mixed at a high temperature in the device, melting the carrier and rapidly cooling it down. The distribution and size of the particles can be regulated at any stage of the liposphere processing by adjusting the microfluidizer's temperature. 15

**h) Solvent Extraction Method**

An aqueous solution of polyvinyl alcohol (PVA) (0.5% w/w) is added as the extraction fluid after the cationic lipid (tripalmitin) and triglyceride (tripalmitin) have been dissolved in the organic solvent (dichloromethane). Pumping the solution and extraction fluid through a static microchannel mixer produces an O/W emulsion. When fine lamellae from the mixing process break down into droplets and spread throughout the extraction aqueous media, lipid microspheres are produced.

**i) Polymeric Lipospheres**

Polymeric biodegradable lipospheres can also be made via solvent or melt processes. Polymeric lipospheres are different from traditional liposphere formulations due to the composition of the inner core of the particles. Conventional lipospheres, such as the ones discussed earlier, consist of a solid hydrophobic fat core composed of neutral fats like tristearin; in polymeric lipospheres, on the other hand, the triglycerides are substituted with biodegradable polymers, such as polylactide (PLD) or PCL. Both kinds of lipospheres are thought to be stabilized by a single layer of phospholipid molecules that are embedded on their surface. 16

**j) Storage of Lipospheres**

The liposphere formulations are kept at room temperature, in the freezer, in the refrigerator, or freeze-dried in an ointment or cream basis. For instant usage, it is best to keep the formulations suspended in an aqueous solution in the refrigerator. 17

**k) Preparation of Nanosized Lipospheres**

The preparation of nanosized lipospheres involves homogenization using sequential filters with smaller pore sizes. Using a dispersible concentrate oil solution, a different technique for in situ synthesis of nanosized lipospheres—particles smaller than 100 nm—has recently been established (18). In this solution, an organic solvent that is miscible with every component is combined with conventional surfactants like Tween and Span to dissolve the medication, triglyceride, phospholipid, and other additives. These organic solvents include N-methyl pyrrolidone (NMP), propanol, propylene glycol, low molecular weight polyethylene glycol (PEG), propylene–ethylene glycol copolymers (Poloxamer), ethoxylated castor oil (Cremophor), and PEG conjugated a-tocopherol. When carefully mixed with an aqueous solution, this clear anhydrous solution spontaneously produces nanoparticles. The formulation components primarily regulate the particle size. Catalytic or anionic nano lipospheres can be created by adding a cationic or anionic lipid to the solution, such as phosphatidyl ethanol amine, stearyl amine, stearic acid, or phosphatidyl acid. 18

1. **CONCLUSION**

If the challenges of transdermal medication administration are properly addressed, it can be a beneficial field. Drug and bioactive substance transport issues might have an innovative answer due to the Lipospheres. Large molecules like peptides, hormones, and antibiotics, as well as other bioactive with poor penetration due to unfavourable physicochemical characteristics, can all be delivered effectively and noninvasively using these vesicles. They also have the potential to deliver drugs with immediate and targeted action. The creation of new, more effective medicines is faced with new obstacles and potential due to the enhanced transport of bioactive chemicals via the skin using vesicular carriers.

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1. **REFERENCES**
2. Dudala TB, Yalavarthi PR, Vadlamudi HC, Thanniru J, Yaga G, Mudumala NL, Pasupati VK. A perspective overview on lipospheres as lipid carrier systems. International journal of pharmaceutical investigation. 2014 Oct;4(4):149.
3. Casey G. Physiology of the skin. Nursing Standard (through 2013). 2002 May 8;16(34):47.
4. Wysocki AB. Skin anatomy, physiology, and pathophysiology. Nursing Clinics of North America. 1999 Dec 1;34(4):777-97.
5. Jain S, Patel N, Shah MK, Khatri P, Vora N. Recent advances in lipid-based vesicles and particulate carriers for topical and transdermal application. Journal of pharmaceutical sciences. 2017 Feb 1;106(2):423-45.
6. Swain S, Beg S, M Babu S. Liposheres as a novel carrier for lipid based drug delivery: current and future directions. Recent Patents on Drug Delivery & Formulation. 2016 Apr 1;10(1):59-71.
7. Chime SA, Onyishi IV. Lipid-based drug delivery systems (LDDS): Recent advances and applications of lipids in drug delivery. Afr. J. Pharm. Pharmacol. 2013 Dec 29;7(48):3034-59.
8. Ijaz H, Qureshi J, Tulain UR, Iqbal F, Danish Z, Fayyaz A, Sethi A. Lipid particulate drug delivery systems: a review. Bioinspired, Biomimetic and Nanobiomaterials. 2018 Feb 27;7(2):109-21.
9. Akki R, Bhattiprolu SS, Vinukonda A, Kathirvel S. An overview on liposheres. World J. Pharm. Res. 2022 Apr 25; 11:217-32.
10. Saxena M. Liposphere-Lipid Based Drug Delivery System For Delivery Of Poorly Water-Soluble Compounds: A Review, World J. Pharm. Res. 10;258-279.
11. Patra CN. Solid lipid-based delivery system for oral delivery of drugs: A review. Asian Journal of Pharmaceutics (AJP). 2018;12(04).
12. Rawat Singh M, Pradhan K, Singh D. Lipid matrix systems with emphasis on lipid microspheres: potent carriers for transcutaneous delivery of bioactives. Current Drug Delivery. 2012 May 1;9(3):243-54.
13. Lawrence MJ. Microemulsions as drug delivery vehicles. Current opinion in colloid & interface science. 1996 Dec 1;1(6):826-32.
14. Andrews LE, Chan MH, Liu RS. Nano-lipospheres as acoustically active ultrasound contrast agents: evolving tumor imaging and therapy technique. Nanotechnology. 2019 Feb 20;30(18):182001.
15. Rawat Singh M, Pradhan K, Singh D. Lipid matrix systems with emphasis on lipid microspheres: potent carriers for transcutaneous delivery of bioactives. Current Drug Delivery. 2012 May 1;9(3):243-54.
16. Khan IU, Serra CA, Anton N, Vandamme T. Microfluidics: a focus on improved cancer targeted drug delivery systems. Journal of controlled release. 2013 Dec 28;172(3):1065-74.
17. Rout A, Mohapatra M, Kumar LA, Patro SK. Recent Trends In Nanoliposphere. Journal of Pharmaceutical Negative Results. 2022 Dec 27:3792-7.
18. Bakliwal AA, Bedse S, Talele SG, Chaudhari GN. Pharmaceutical and Nano Sciences.
19. Elgart A, Cherniakov I, Aldouby Y, Domb AJ, Hoffman A. Lipospheres and pro-nano lipospheres for delivery of poorly water soluble compounds. Chemistry and Physics of Lipids. 2012 May 1;165(4):438-53.